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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,610	01/27/2004	Gregory J. LaRosa	1855.1052-029	3808

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EXAMINER	
BOESEN, AGNIESZKA	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
11/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,610	LAROSA ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-13,15,16,18-22 and 66-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-13,15,16,18-22 and 66-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 12, 2007 has been entered.

Claims 1, 3-5, 7-13, 15, 16, 18-22, and 66-85 are pending and under consideration in this Office action.

Restriction/Election

Applicant's election of species of SEQ ID NO: 12 representing the humanized immunoglobulin light chain variable region and SEQ ID NO: 17 representing the humanized immunoglobulin heavy chain variable region is acknowledged.

Priority

Acknowledgment is made for priority to a DIV application, 09/840,459, (which is a US Patent 6,696,550), which is a CON of PCT/US01/03537, which is a CIP of 09/497625, (which is a US Patent 6,727,349), which is a CIP of 09/359193, (which is a US Patent 6,352,832), which is a CIP of 09/121781 (which is a US Patent 6,312,689). The limitations of the SEQ ID NO: 12 SEQ ID NO: 17, SEQ ID NO: 98, and SEQ ID NO: 97 are not seen in the applications 09/359193, or 09/121781. As such claims 3, 4, 7-12, 67-79, and 82-85 are granted the priority date of February 2, 2000. Claims 1, 5, 13, 15, 16, 18-22, 66, and 80 are granted priority of July 23, 1998.

Claim Rejections - 35 USC § 112

Rejection of claims 1, 3, 5, 7, 9, 11, 13, 15, 16, 18, 19-22, and 66-85 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** in view of Applicant's arguments.

Rejection of claims 1, 3, 5, 7, 9, 11, 13, 15, 16, 18, 19-22, and 66-85 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is **withdrawn in** view of Applicant's arguments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7-13, 15, 16, 18-22, and 66-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Biological Deposit

It is apparent that the antibodies 1D9, HF 21/28, and 4B4'CL are required to practice the claimed invention because they are a necessary limitation for the success of the invention as stated in the claims. The antibodies recited in the claims must be known and readily available to

the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the hybridoma cell lines producing the antibodies 1D9, HF 21/28, and 4B4'CL. See 37 CFR 1.802.

It is acknowledged that the sequences of the variable heavy (SEQ ID NOs: 17, 18, 19, and 20) and light (SEQ ID NO: 12, 13, 14, 15, and 107) regions of the claimed antibodies have been provided in the present specification. It is understood that the claimed sequences of the light and heavy variable antibody regions originated from the murine 1D9 antibody. However in order to produce a functional antibody of the present invention, the light chain framework region from the human HF 21/28 antibody and the heavy chain framework region from the human 4B4'CL antibody are required. Therefore the access to antibodies HF 21/28, and 4B4'CL is necessary in order to successfully practice the present invention. Because independent claims 1 and 5 broadly recite an "antigen-binding fragment comprising CDR1, CDR2, and CDR3 of the light and heavy chain of the murine 1D9 antibody" the access to the 1D9 antibody is required to practice the invention of claims 1 and 5.

Without a publicly available deposit of the hybridoma cell line producing the antibodies 1D9, HF 21/28, and 4B4'CL, one of ordinary skill in the art could not be assured of the ability to practice the present invention. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, different V_H chains can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when

different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Therefore, it would require undue experimentation to reproduce the claimed antibodies 1D9, HF-21/28, and 4B4'CL.

It is acknowledged that the specification provides the information with regard to the biological deposit, (see below). However, because the listed ATCC accession numbers do not correspond with the names of the claimed antibodies (besides the 1D9 antibody), the skilled artisan would be unable to request the hybridomas (from the ATCC) and make the antibodies necessary to practice the present invention.

> [0061] "Hybridoma cell lines producing antibodies according to the present invention were deposited on Jul. 17, 1998, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, Mass. 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, Mass. 02139, U.S.A.), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Va. 20110, U.S.A., under Accession Nos. HB-12549 (1D9) and HB-12550 (8G2). The present invention also pertains to the hybridoma cell lines deposited under ATCC Accession No. HB-12549 and ATCC Accession No. HB-12550, as well as to the monoclonal antibodies produced by the hybridoma cell lines deposited under ATCC Accession Nos. HB-12549 and HB-12550."
>
> [0136] "The present invention also pertains to the hybridoma cell lines deposited under ATCC Accession Nos. HB-12549 and HB-12550, as well as to the monoclonal antibodies produced by the hybridoma cell lines deposited under ATCC Accession Nos. HB-12549 and HB-12550."

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating

that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Scope of Enablement Rejection

Claims 1, 3-5, 7-13, 15, 16, 18-22, and 66-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding a humanized immunoglobulin light chain or antigen-binding fragment thereof comprising CDR1, CDR2 and CDR3 of the light chain of murine 1D9 antibody and a human light chain framework region from the light chain of the human HF 21/28 antibody, wherein the antibody has binding specificity for CCR2, does not reasonably provide enablement for an nucleic acid encoding an antibody without known binding specificity.

The specification, while being enabling for an isolated nucleic acid encoding a humanized immunoglobulin heavy chain or antigen-binding fragment thereof comprising CDR1, CDR2 and CDR3 of the heavy chain of murine 1D9 antibody and a human heavy chain framework region from the heavy chain of the human HF 21/28 antibody, wherein the antibody has binding specificity for CCR2, does not reasonably provide enablement for an isolated nucleic acid encoding an antibody without known binding specificity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The independent claims 1 and 22 are drawn to an isolated nucleic acid encoding a humanized immunoglobulin light chain or antigen-binding fragment thereof comprising CDR1, CDR2 and CDR3 of the light chain of murine 1D9 antibody and a human light chain framework region from the light chain of the human HF 21/28 antibody.

The independent claims 5 and 66 are drawn to an isolated nucleic acid encoding a humanized immunoglobulin heavy chain or antigen-binding fragment thereof comprising CDR1,

CDR2 and CDR3 of the heavy chain of murine 1D9 antibody and a human light chain framework region from the heavy chain of the human 4B4'CL antibody.

The claims are rejected because the specification does not provide sufficient enablement to make and use the presently claimed nucleic acids without knowing the antigen specificity of an antibody being encoded by the claimed nucleic acids. The skilled artisan would not know how to make the presently claimed nucleic acids without the knowledge of the antigen binding specificity of the heavy and/or light chain of the present invention. The claims recite "an antigen-binding fragment", however the claims do not specify the antigen to which the antibody should bind. Thus the claims broadly read on any antigen, and therefore encompass nucleic acids that encode light and heavy chains without specificity to a particular antigen. Without the knowledge of a specific antigen to which the antibody should bind, the skilled artisan would be unable to make and use the nucleic acids of the present invention. Furthermore, the nucleic acids encoding proteins without antigen specificity would not be useful in the presently claimed methods of preparing the humanized immunoglobulin. Thus the skilled artisan would not be able to practice the claimed methods with a reasonable expectation of success.

The specification discloses that the present antibody has specificity to CCR2 molecule, and that the complete functional antibody of the current invention comprises the variable heavy and variable light chains comprising six CDR regions from 1D9 antibody and the framework regions from human antibodies HF 21/28 and 4B4'CL. The current claims do not recite all the components of a functional antibody, or the binding specificity of the claimed antibody. Amending the claims to recite the antibody specificity would help overcome the present rejection.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Li et al. (Biochemistry 2000. 39:6296-6309) in a study of three-dimensional structures of an antigen-bound Fab fragment of a monoclonal antibody, disclose that all six CDRs of the Fab variable domains are involved in binding the antigen (see entire document, particularly page 6301). Thus it is necessary that six complementarity-determining regions (CDRs) must be present in an antibody in order for an antibody to bind antigen.

As noted above the present claims are broader than the enabling disclosure. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Therefore considering the knowledge in the art with regard to the structure of the antibody antigen binding region, and the unpredictable changes in antibody binding affinity resulting from minor alterations in the CDR regions, it is apparent that the ordinary artisan would be unable to practice the present invention to the full extend as claimed.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 22 and 66 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims are drawn to a fused gene encoding a humanized immunoglobulin light and heavy chain. Claims as written, does not sufficiently distinguish over genes as they naturally exist because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the present case a fused gene could be a part of a human chromosome present in a cell of a human. The scope of the claims, therefore, encompasses a human being, which is non-statutory subject matter. Amending the claims to recite "a fused nucleic acid" or "an isolated fused gene" can help overcome this rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 13, 15, 16, 18-22, 66, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-74 of U.S. Patent No.6,696,550 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to an isolated nucleic acid encoding a humanized immunoglobulin light and heavy chain of the murine 1D9 antibody and the framework regions from the HF 21/28 and 4B4'CL antibodies and the patented claims are drawn to antibodies with binding specificity for CCR2, wherein the antibody binding regions are from the 1D9 antibody and the framework regions are from the HF 21/28 and 4B4'CL antibodies. The nucleic acids of the present invention are obvious over the antibodies encoded by the nucleic acids of the present invention.

Claims 1, 5, 13, 15, 16, 18-22, 66, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, and 11-38 of U.S. Patent No. 6,312,689 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to an isolated nucleic acid encoding a humanized immunoglobulin light and heavy chain of the murine 1D9 antibody and the framework regions from the HF 21/28 and 4B4'CL antibodies and the patented claims are drawn to antibodies with binding specificity for CCR2, wherein the antibody binding regions are from the 1D9 antibody. The nucleic acids of the present invention are obvious over the antibodies encoded by the nucleic acids of the present invention.

Claims 1, 5, 13, 15, 16, 18-22, 66, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-51 of U.S. Patent No. 6,727,349 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to an isolated nucleic acid encoding a humanized immunoglobulin light and heavy chain of the murine 1D9 antibody and the framework regions from the HF 21/28 and 4B4'CL antibodies and the patented claims are drawn to antibodies with binding specificity for CCR2, wherein the antibody binding regions are from the 1D9 antibody and the framework regions are from the HF 21/28 and 4B4'CL antibodies. The nucleic acids of the present invention are obvious over the antibodies encoded by the nucleic acids of the present invention.

Conclusion

SEQ ID NO: 12 and SEQ ID NO: 17 are free of prior art of record.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday – Friday 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AB

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